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(57) Abstract

The invention relates to compositions such as body and hair cleansing products, in particular shampoos, comprising dichlorophenyl imidazoldioxolan and methods for using such compositions to alleviate the symptoms associated with dandruff, seborrheic dermatitis, acne, and psoriasis.

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METHODS FOR USING COMPOSITIONS CONTAINING DICHLOROPHENYL IMIDAZOLDIOXOLAN TO TREAT SEBORRHEIC DERMATITIS, DANDRUFF, PSORIASIS, AND ACNE, AND COMPOSITIONS THEREOF

CROSS-REFERENCE TO RELATED APPLICATION

This Application claims the benefit of United States Provisional Application Number 60/051,418 filed on 2 July 1997, which is incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

1. FIELD OF THE INVENTION

The invention relates to methods for using compositions comprising dichlorophenyl imidazoldioxolan in treating the symptoms associated with seborrheic dermatitis, dandruff, psoriasis, and acne and the compositions used therein.

2. DESCRIPTION OF THE PRIOR ART

Traditional approaches for treating skin and scalp diseases such as dandruff, seborrheic dermatitis, psoriasis, and acne include the topical administration of an agent capable of :1) inhibiting microorganism growth on the skin surface; 2) reducing skin surface irritation; and/or 3) reducing the sebum production on the skin surface.

In the first approach for treating such diseases via inhibition of the growth of microorganisms, particularly that of *Malassezia furfur (Pityrosporum ovale)*, products have incorporated one or more of the many known *Malassezia furfur* inhibitors such as ketoconazole, selenium sulfide, zinc pyrithione, coal tar and piroctone olamine.

United States Patent No. 4,569,935 disclosed that ketoconazole was useful in the topical treatment of psoriasis and seborrheic dermatitis. Shampoos containing 2% ketoconazole are known to show a beneficial effect in treating seborrheic dermatitis after topical application. It is further known that stable shampoos which exhibit better cosmetic attributes such as lathering and conditioning have been formulated to contain less than 2 % active ingredient . See United States Patent No. 5,456,851.

A second known approach for treating one or more of the above-mentioned diseases involves the reduction of the symptoms, i.e. scaling, flaking, and itching,

associated with these diseases. One such method is via the topical application of a keratinolytic agent, i.e. one which is effective in "sloughing -off" the excess cells which build up on the surface of the skin. See IL 113057. Other methods for reducing the itching, irritation and skin dryness involve the regulation of the types and amounts of detergents used therein. See WO-96/29983 (mild aqueous detergent compositions comprising from about 4 to about 12 % by weight of an anionic surfactant, an amphoteric surfactant at a level of at least about 0.75 parts by weight per part by weight of said anionic surfactant, and one or more of 11 listed therapeutic agents).

Although coal tar is only somewhat effective in inhibiting *Malassezia furfur* growth, it is known to be effective in suppressing DNA synthesis and thus also in inhibiting cell division. Since cell proliferation and buildup create symptoms of scaling, flaking, and itching, the ability of coal tar to inhibit cell division appears to alleviate these symptoms. For example, WO-96/29045 generically discloses combinations of cytotoxic agents and antifungal agents for the treatment of seborrheic dermatitis of the scalp; however, it specifically discloses the combined use of an unidentified composition comprising 1.8 % coal tar and an unidentified solution comprising 2% ketoconazole.

A third approach for treating seborrheic dermatitis, dandruff, psoriasis, and acne is via the reduction of sebum production on the skin surface, a frequent symptom of those who suffer from these diseases. It is believed that the presence of a high degree of sebum trapped on the skin surface by the proliferation of surface skin cells may provide a beneficially nurturing environment for microorganisms. Agents such as alcohols, solvents, and surfactants have been incorporated into various treatments for the purpose of reducing sebum production; however, these agents are very irritating to the skin and are ineffective against inhibting the growth of *M. furfur*.

It would be beneficial to have a composition for treatment of seborrheic dermatitis, dandruff, psoriasis, acne and the like which not only inhibited microorganism growth, but which also effectively sloughed-off excess skin cells from the skin surface and reduced the sebum-production on the skin surface without any of the above disadvantages.

SUMMARY OF THE INVENTION

In accordance with this invention, there is provided a method for treating seborrheic dermatitis, dandruff, and psoriasis comprising, consisting essentially of or consisting of:

a) applying to the skin or hair an effective amount of a composition comprised of

1) dichlorophenyl imidazoldioxolan; and

2) a therapeutic component selected from salicylic acid, coal tar and derivatives thereof, piroctone olamine (Octopirox), selenium sulfide, ciclopirox olamine, or mixtures thereof.

Another embodiment of the present invention is directed to a composition comprising, consisting essentially of or consisting of:

a) dichlorophenyl imidazoldioxolan; and

b) a therapeutic component selected from salicylic acid, coal tar and derivatives thereof, piroctone olamine (Octopirox), selenium sulfide, ciclopirox olamine, or mixtures thereof.

This composition may be combined with art known body or hair cleansing product ingredients to form various body and hair cleansing products such as soaps, gels, and shampoos.

Yet another embodiment of this invention is directed to a process for preparing a body and hair cleansing formulation comprising, consisting essentially of or consisting of:

(a) mixing an anionic surfactant and deionized water under conditions sufficient to produce a first mixture;

(b) mixing an effective amount of dichlorophenyl imidazoldioxolan and an antioxidant with the first mixture under conditions sufficient to produce a second mixture;

(c) cooling the second mixture to a sufficient temperature before the addition of a therapeutic component thereto;

(d) mixing the therapeutic component with the cooled second mixture under conditions sufficient to produce a third mixture;

(e) mixing a buffer and an amphoteric surfactant with the third mixture under conditions sufficient to produce a fourth mixture.

In yet another embodiment is a method for inhibiting the growth of bacterium on the surface of skin comprising, consisting essentially of, and/or comprising:

topically applying to the skin an effective amount of a composition comprised of dichlorophenyl imidazoldioxolan.

We have unexpectedly found that dichlorophenyl imidazoldioxolan and compositions comprised thereof were superior in inhibiting the growth of microorganisms such as *M. furfur* and *Propionibacterium acnes (P. acne)*. Moreover, the combination of dichlorophenyl imidazoldioxolan with one or more therapeutic components often provided

significant improvement and/or synergism over prior art shampoos and cleansers which contained the components alone. As a consequence thereof, the concentration of one or both of the different types of components can be lowered, thus increasing its tolerability by the user.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

In the following description, the invention is illustrated using shampoos as examples, but it will be evident to a person skilled in the art that the combinations according to the present invention can be utilized just as well in other body and hair cleansing products including baths, bars, gels, and the like.

The term, "MEA" shall include a mono-ethanolamide of formula RCO-NH-CH_2CH_2-OH; "DEA" shall include a di-ethanol amide of formula RCO-N(CH_2CH_2-OH)$_2$; "MIPA" shall include a mono-isopropanol amide of formula RCO-NH-CH_2-CHOH-CH_3, wherein each RCO-group is a fatty acid residue, such as a C_{13-19} alkylcarbonyl or C_{13-19} alkenylcarbonyl group; and "TEA" shall mean triethanolammonium. As used herein, the term "amphoteric" shall mean: 1) molecules that contain both acidic and basic sites such as, for example, an amino acid containing both amino (basic) and acid (e.g., carboxylic acid, acidic) functional groups; or 2) zwitterionic molecules which possess both positive and negative charges within the same molecule. The charges of the latter may be either dependent on or independent of the pH of the composition.

Dichlorophenyl imidazolodioxalan is commercially available from Janssen Pharmaceutica, N.V., under the tradename, "Elubiol." Although the amount of dichlorophenyl imidazoldioxolan used in the composition of the present invention may depend upon, for example, the type of symptoms present and the amount of other ingredients combined therewith, one skilled in the art could readily determine, without undue experimentation, that the dichlorophenyl imidazoldioxolan may be used in an amount, based upon the total weight of the composition, from about 0.1 % to about 2 %, preferably from about 0.25 % to about 1 %, and more preferably from about 0.25% to about 1 %. As will be explained further, at the lower end of this range, special precautions may have to be taken in order to ensure that the shampoo does not lose its efficacy due to degradation of the antifungal compound upon storage. Concentrations higher than those indicated do not improve the treatment of the conditions any further, and are on the whole more detrimental than beneficial.

The composition of the present invention further includes a therapeutic component effective in achieving a therapeutic result in the treatment of dandruff, seborrheic

dermatitis, and psoriasis selected from salicylic acid, coal tar and derivatives thereof such as anthralin, piroctone olamine (Octopirox), selenium sulfide, ciclopirox olamine, other known anti-dandruff agents or mixtures thereof. Salicylic acid is the therapeutic component of choice. Although the amount of the therapeutic component may vary for reasons similar to those set forth above, one skilled in the art could readily determine, without undue experimentation, that the therapeutic component may be used in an amount, based upon the total weight of the composition, from about 0.5 % to about 3 %, and preferably from about 1 % to about 2 %.

In a preferred embodiment, the dichlorophenyl imidazoldioxolan and the therapeutic component(s) are present in quantities which produce a significant improvement and/or mutual synergistic effect on the inhibition of the growth of dermatophyte fungi, in particular the species associated with dandruff and seborrheic dermatitis, i.e. *Malessezia furfur (Pityrosporum ovale)*, but also on the growth of other species such as *Epidermophyton, Microsporum,* and *Trichophyton* spp. associated with, for example, tinea capitis, tinea corporis and the like. The ratio of the quantities of the dichlorophenyl imidazoldioxolan and the therapeutic component(s) will depend on the nature of the therapeutic component(s) and on the target species. Particularly, it is contemplated that the weight : weight ratio between the dichlorophenyl imidazoldioxolan and the therapeutic component may range from about 0.1 : 3 to about 2 : 0.5 , and preferably from about 0.25 : 2 to about 0.5 : 1.0. Particularly effective in inhibiting the proliferation of dermatophyte fungi, and especially *Malessezia furfur*, is the combination of dichlorophenyl imidazoldioxolan with salicylic acid in a weight ratio of from about 0.5 : 2.0 to about 1: 1. Unexpectedly, this combination also produces a mutually synergistic effect on the pathogenic yeast, *Candida albicans*.

In another preferred embodiment, the composition may contain dichlorophenyl imidazoldioxolan, salicylic acid, and, based upon the total weight of the composition, from about 0% to about 1%, preferably from about 0.25 % to about 1%, and more preferably from about 0.50 % to about 0.75 % piroctone olamine (Octopirox).

The shampoos according to the present invention can conveniently be formulated using art-known shampoo bases; the art-known shampoo ingredients comprise one or more of a surfactant, a foaming agent, a thickener sufficient to give the final formulation a viscosity in the range of about 4,000 to about 9,000 mPa.s at room temperature, a preservative system, an anti-oxidant system, and acid or base or buffer sufficient to give

the shampoo a pH in the range of from about 3 to about 8. A single ingredient can have two or more functions, e.g. surfactant and foaming agent.

Suitable surfactants for use in the shampoos according to the present invention include any commercially available nonionic surfactant, amphoteric surfactant, anionic surfactant, or mixtures thereof.

One class of suitable nonionic surfactants useful in the present invention include polyoxyethylene derivatives of polyol esters, wherein the polyoxyethylene derivative of polyol ester (1) is derived from (a) a fatty acid containing from about 8 to about 22, and preferably from about 10 to about 14 carbon atoms, and (b) a polyol selected from sorbitol, sorbitan, glucose, α-methyl glucoside, polyglucose having an average of about 1 to about 3 glucose residues per molecule, glycerine, pentaerythritol and mixtures thereof, (2) contains an average of from about 10 to about 120, and preferably about 20 to about 80 oxyethylene units; and (3) has an average of about 1 to about 3 fatty acid residues per mole of polyoxyethylene derivative of polyol ester.

Another class of suitable nonionic surfactants includes long chain alkyl glucosides or polyglucosides, which are the condensation products of (a) a long chain alcohol containing from about 6 to about 22, and preferably from about 8 to about 14 carbon atoms, with (b) glucose or a glucose-containing polymer. The alkyl glucosides have about 1 to about 6 glucose residues per molecule of alkyl glucoside.

Amphoteric surfactants suitable for use in the present invention include, but are not limited to amphocarboxylates, alkyl betaines, amidoalkyl betaines, amidoalkyl sultaines, amphophosphates, phosphobetaines, pyrophosphobetaines, carboxyalkyl alkyl polyamines and mixtures thereof.

Suitable anionic surfactants may be selected from alkyl sulfates, alkyl ether sulfates, alkyl monoglycerylether sulfates, alkyl monoglyceride sulfates, alkyl monoglyceride sulfonates, alkyl sulfonates, alkylaryl sulfonates, alkyl sulfosuccinates, alkyl ether sulfosuccinates, alkyl sulfosuccinamates, alkyl amidosulfosuccinates, alkyl carboxylates, alkyl amidoethercarboxylates, alkyl succinates, fatty acyl sarcosinates, fatty acyl amino acids, fatty acyl taurates, fatty alkyl sulfoacetates, alkyl phosphates, and mixtures thereof.

Preferred surfactants include sodium olefin sulfonates wherein the olefin has from about 14 to about 16 carbon atoms, sodium lauryl sulfate, TEA lauryl sulfate, sodium laureth sulfate, cocamidopropylamine oxide, lauryl amine oxide, lauramido DEA, cocamidopropyl betaine, lauryl dimethyl betaine, cocodimethyl sulfo-propyl betaine, sodium cocoyl sarcosinate, disodium oleamido MIPA sulfosuccinate, disodium cocamido MIPA

sulfosuccinate, disodium laureth sulfosuccinate, cocoamphocarboxy-glycinate, disodium oleamido MEA sulfosuccinate, amine glycinates, amine propionates and amine sultaines, and mixtures thereof, with sodium olefin sulfonates being most preferred.

In a preferred embodiment of the present shampoos, a mixture of two or more different surfactants, more preferably a mixture of anionic surfactants and amphoteric surfactants, and in particular sodium laureth sulfonate and sodium cocoyl sarcosinate, or sodium lauryl sulfonate, sodium laureth sulfonate, TEA lauryl sulfonate, cocoamidopropylamine oxide, and cocamidopropyl betaine, may be used.

In the compositions according to the present invention, the total amount of surfactants may range from, based upon the total weight of the composition, from about 30% to about 60%, and preferably from about 40% to about 50%. Preferably the shampoos contain, based upon the total weight of the shampoo, from about 15% to about 30%, and preferably from about 20% to about 25% of an anionic surfactant, from about 5% to about 20%, and preferably from about 10% to about 15% of a non-ionic surfactant, and from about 10% to about 30%, and preferably from about 20% to about 25% of an amphoteric surfactant. Preferably, the weight of amphoteric surfactants is less than 15 % by weight of the total amount of surfactants. Most preferably, the shampoo may comprise, based upon the total weight of the composition, from about 20 % to about 25% of an anionic surfactant such as sodium olefin sulfonate, and from about 20 % to about 25% of an amphoteric surfactant comprising, based upon the total weight of the amphoteric surfactant, from about 1.0 % to about 5.0% cocamidopropylamine oxide and from about 20% to about 25% cocamidopropyl betaine.

Suitable foaming agents (foam boosters and stabilizers) for use in the composition of the present invention include, but are not limited to fatty acid mono- and dialkanol-amides and mixtures thereof. Examples of such amides are cocamide MEA, cocamide DEA, oleamide MEA, oleamide DEA and mixtures thereof. The foaming agent may be present in a range from about 0 to about 10 % (w/w), preferably from about 2 to about 6 % (w/w), in particular about 4 to about 5 % (w/w). These ingredients typically also have a thickening effect on the formulation.

Suitable preservatives for use in the present shampoos are dermatologically acceptable preservatives, e.g. sodium EDTA, methylparaben, propylparaben, butylparaben, ethylparaben, imidazolidinyl urea, diazolidinyl urea, phenoxyethanol, quaternium 15, citric acid, preferably in combinations with one another. Sodium EDTA and citric acid also

function as chelating agents. The preservatives are used in an amount effective to retard degradation of the final composition in order to give adequate shelf life.

When the concentration of dichlorophenyl imidazoldioxolan is at the lower end of the ranges mentioned hereinabove, the addition of a carefully controlled amount of an antioxidant selected from the group consisting of butylated hydroxytoluene ("BHT"), butylated hydroxyanisole ("BHA"), ascorbic acid, N-acetyl-cysteine, and sodium metabisulfite effectively stabilizes the dichlorophenyl imidazoldioxolan present in the shampoo against degradation during accelerated aging for 13 weeks at 50°C, which is considered to be predictive of performance during storage at ambient temperatures for two years. See US 5,456,851. Effective stability is considered to be a loss of active ingredient during storage of not more than about 10 percent. The proportion of BHT or BHA that has been found to be most effective is within the range of from about 0.01 % to about 1 % (w/w). Proportions greater than this amount do not stabilize dichlorophenyl imidazoldioxolan as effectively for the 13-week accelerated aging period. However, it is well recognized by government regulatory agencies and in the pharmaceutical and cosmetic industries that stability testing for 13 weeks at 50°C is quite sufficient to predict product stability during normal shelf life storage for two (2) years at room temperature. It is also equally important that, for safety reasons (that is, to minimize the potential for skin sensitization), it is desired to use as small an amount as possible of BHT or BHA.

Since shampoo users expect a shampoo to be slightly viscous, one or more thickeners are often included in the formulation which give it a viscosity in the range of 4,000 to 9,000 mPa.s at room temperature. A suitable thickener is a carbomer or polycarboxylic acid, such as Carbopol ™ 1342, which is thickened by the addition of sodium hydroxide or sodium chloride at the end of the preparation. Other suitable thickeners are xanthan gum, veegum, and the foaming agents mentioned hereinabove, preferably cocamide MEA. Although the amount of thickener used will depend upon the viscosity desired, typically the amount of thickener used may range, based upon the total weight of the shampoo, from about 0 % to about 2%, and preferably from about 0.2% to about 1.3%.

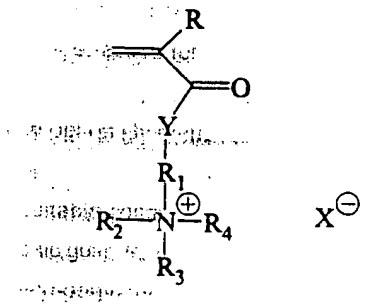
Suitable pH adjusters or buffers for use in the present invention include, but are not limited to sodium citrate, citric acid, and mixtures thereof. The pH of the shampoos according to the present invention are conveniently established using dermatologically acceptable acids, bases and buffers. The pH can range from about 3.0 to about 8.0, but

preferably is in the range of about 3.5 to about 5.0, in particular from about 3.7 to about 4.2.

Optional solubilizers for use in the present invention include, but are not limited to hexylene glycol, propylene glycol, butylene glycol and mixtures thereof. These solubilizers should be used in an amount effective for dissolving substantially all of the solids in a given solution.

The shampoo may optionally comprise a conditioner in an amount, based upon the total weight of the shampoo, from about 0 to about 5%, and preferably from about 1% to about 3%. Examples of suitable conditioners include, but are not limited to a cationic cellulose derivative; a cationic guar derivative; silicon substances such as cyclomethicone, dimethicone, and a glyceryl-derivative such as linoleamidopropyl polyglycol dimonium chloride, and mixtures thereof; a homopolymer or copolymer of a cationic monomer selected from:

a. a monomer having formula I.



I.

wherein

R is H or CH_3,

Y is O or NH,

R_1 is an alkylene group having from about 2 to about 6, and preferably from about 2 to about 3 carbon atoms,

R_2, R_3 and R_4 are each independently an alkyl group having from about 1 to about 22, and preferably from about 1 to about 4 carbon atoms, and

X is a monovalent anion selected from halide and alkyl sulfate, or

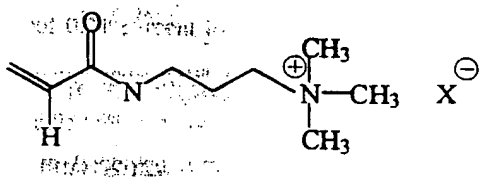
b. diallyldimethylammonium chloride; or mixtures thereof.

The amount of each conditioner component may range, based upon the total weight of the composition, from about 0.01 percent to about 1.0 percent, preferably from about 0.01 percent to about 0.5 percent, and more preferably from about 0.01 to about 0.2 percent.

Preferably, the cationic cellulose derivative includes a polymeric quaternary ammonium salt such as polyquaternium-7, polyquaternium -22, polyquaternium-10, or mixtures thereof with polyquarternium 22 being preferred.

The cationic guar derivative is preferably a guar hydroxypropyltrimonium chloride, available commercially from Rhone-Poulenc Inc., of Cranbury, New Jersey under the tradename, "Jaguar C-17."

Another preferred cationic polymer includes those compounds derived from acrylamidopropyl trimonium chloride which has the formula:



and more preferably is the copolymer of this monomer with acrylamide, the latter of which is available commercially from Allied Colloids, of Suffolk, Virginia under the tradename, "Salcare SC60."

Other preferred cationic conditioning polymers are those derived from the monomer diallyldimethylammonium chloride. The homopolymer of this monomer is Polyquaternium-6, which is available commercially form Allied Colloids of Suffolk, Virginia under the tradename, "Salcare SC30." The copolymer of diallyldimethylammonium chloride with acrylamide is known as Polyquaternium-7, and is also available from Allied Colloids under the tradename "Salcare SC10."

The shampoo may optionally comprise pearlizing agents in an amount, based upon the total weight of the shampoo, of from about 0% to about 3%, and preferably from about

1% to about 1.5%. Examples of suitable pearlizing agents include, but are not limited to, ethylene glycol distearate, ethylene glycol monostearate and mixtures thereof.

Optionally, the shampoos may further comprise one or more fragrances and/or colorants.

The composition should be applied in an amount effective to ameliorate the symptoms associated with dandruff, seborrheic dermatitis, psoriasis, and/or acne. As used herein "amount effective" shall mean an amount sufficient to cover the region of skin surface where the symptom exists and to ameliorate the symptoms associated with the respective disease.

The composition should be topically applied to affected body parts at regular intervals, and preferably from about 1 to about 7 times per week. More preferably, the composition is applied more frequently during the initial stages of treatment, e.g. from about 4 to about 7 times per week until the desired effect is achieved, then less frequently when maintenance is desired, e.g. from about 1 to about 2 times per week. The composition may be applied to the desired area in the form of, for example, a lotion, cream, gel or the like which is designed to be left on the skin and not washed shortly after application. Alternatively, the composition may be applied to the desired area in the form of, for example, a lotion, cream, gel, soap, shampoo or the like which is designed to be rinsed off within a given amount of time after application.

In a preferred embodiment wherein the composition is incorporated into a shampoo, the shampoo is applied to wet hair, and the hair is washed in accordance with known practices. More preferably, the composition remains on the hair for greater than about 0 to about 10 minutes, and preferably from about 4 to about 7 minutes before rinsing.

In the present invention we have unexpectedly found that when compositions comprising dichlorophenyl imidazoldioxolan, a known sebum-reducing agent, see WO-93/18743, were topically applied to the skin or hair of a mammal, the proliferation of *Malassezia furfur* and *Propionibacterium acnes* was significantly inhibited. Therefore, since compositions comprising dichlorophenyl imidazoldioxolan not only possess sebum-reducing properties, but it also possess superior *Malassezia furfur* and *Propionibacterium acnes* growth inhibition properties, they are superior relative to other known therapeutic agents in ameliorating the symptoms associated with dandruff, acne, and the like. Further, when such compositions also include salicylic acid, a known keratinolytic agent, the resulting composition possesses properties which are effective for treating dandruff and the like via all three traditional approaches.

The invention illustratively disclosed herein suitably may be practiced in the absence of any component, ingredient, or step which is not specifically disclosed herein. Several examples are set forth below to further illustrate the nature of the invention and the manner of carrying it out. However, the invention should not be considered as being limited to the details thereof.

EXAMPLES

Example 1: Preparation of Shampoo Base

467 g of purified water and 250 g of "Witconate AOS" surfactant (containing approximately 39% of sodium C14-C16 olefin sulfonate) available from Witco, Corporation were added into a suitable mechanical mixing vessel under ambient temperature and pressure conditions. After the vessel's propeller speed was set at 50 rpm, the internal temperature of the mixture was heated to 70 °C, and the internal pressure of the vessel was increased to 1 bar. After stirring the mixture for about 15 minutes while maintaining a constant internal temperature and pressure, the mixture was then cooled to about 45 °C before the addition of 5 g of sodium citrate, 5 g of "Phospholipid EFA " compound (containing approximately 30% linoleamidopropyl PG dimonium chloride) available from Mona Industries, Incorporated, and 3 g of hexylene glycol thereto.

After stirring the resulting mixture for about 15 minutes while maintaining a constant internal temperature and pressure, 240 g of "Chembetaine" surfactant (containing approximately 30% of cocamidopropyl betaine) available from Chemron Corporation, 10 g of "Standamox CAW" compound (containing approximately 30% of cocamidopropylamine oxide) available from Henkel Corporation, and 20 g of polyquaternium-22 available from Calgon Corporation under the tradename "Merquat 280" were added with stirring thereto. The resulting mixture was mixed for an additional 20 minutes at a constant temperature and pressure. The internal temperature of the mixture was then reduced to about 35 °C before adding sufficient water qs to account for any water loss.

The weight percentages of the components used in this example are illustrated in Table 1 below:

Table 1: Shampoo Formulations

Ingredients	Ex. 1: Shampoo Base	Ex. 2: Base & DI* at pH 4	Ex. 2: Base & DI* at pH 7	Ex. 3: Base, Salicylic Acid, & Piroctone olamine	Ex. 4: Base, DI*, Salicylic Acid, & Piroctone olamine
purified water	79.80	79.30	79.30	77.05	76.55
sodium olefin sulfonate	9.75	9.75	9.75	9.75	9.75
dichlorophenyl imidazoldioxolan	—	0.50	0.50	—	0.50
salicylic acid	—	—	—	2.00	2.00
sodium citrate	0.50	0.50	0.50	0.50	0.50
linoleamidopropyl PG dimonium chloride	0.15	0.15	0.15	0.15	0.15
hexylene glycol	0.30	0.30	0.30	0.30	0.30
cocamidopropyl betaine	7.20	7.20	7.20	7.20	7.20
cocamidopropyl-amine oxide	0.30	0.30	0.30	0.30	0.30
Polyquaternium-22	2.00	2.00	2.00	2.00	2.00
piroctone olamine	—	—	—	0.75	0.75
Total	100.00	100.00	100.00	100.00	100.00

* = dichlorophenyl imidazoldioxolan

Example 2: Preparation of Shampoo Base Containing Dichlorophenyl Imidazoldioxolan

The process set forth in Example 1 is repeated, except that 5g of dichlorophenyl imidazoldioxolan available from Janssen Pharmaceutica N. V. under the tradename "Elubiol" was added to the mixture of purified water and sodium olefin sulfonate.

The resulting mixture was then mixed for about 40 minutes until all of the solids were substantially dissolved before the addition of sodium citrate, linoleamidopropyl PG dimonium chloride and hexylene glycol thereto. The pH of the resulting mixture was about 7. The pH was adjusted to about 4 with the use of qs amount of citric acid. The weight percentages of the components used in this example are illustrated in Table 1.

Example 3: Preparation of Shampoo Base Containing Salicylic Acid and Piroctone olamine.

The water - sodium olefin sulfonate mixture was made in accordance with the process set forth in Example 1, with the exception that 440 g of purified water was used.

After stirring the mixture for about 40 minutes while maintaining a constant internal temperature and pressure therein, the mixture was then cooled to about 50 °C before the addition of 20 g of salicylic acid available from Spectrum Chemicals was added thereto with stirring for about 15 minutes until substantially all of the solids were dissolved. Temperature and pressure remained constant.

5 g of sodium citrate, 5 g of the "Phospholipid EFA " compound of Example 1, and 3 g of hexylene glycol were then stirred into the mixture. After stirring the mixture for about 15 minutes while maintaining a constant internal temperature and pressure, 240 g of the "Chembetaine" surfactant of Example 1, 10 g of the "Standamox CAW" compound of Example 1, 20 g of the polyquaternium-22 of Example 1, and 7.5 g of piroctone olamine available from Hoechst under the tradename "Octopirox," were added with stirring thereto. After mixing the resulting mixture for an additional 20 minutes at a constant temperature and pressure, the internal temperature of the mixture was then reduced to about 35 °C before sufficient water was added thereto qs to account for any water loss. The weight percentages of the components used in this example are illustrated in Table 1.

Example 4: Preparation of Shampoo Base Containing Dichlorophenyl Imidazoldioxolan, Salicylic Acid, and Piroctone olamine.

The process set forth in Example 4 was repeated, except that 5g of the dichlorophenyl imidazoldioxolan of Example 2 was stirred into the mixture of purified water

and sodium olefin sulfonate, and the resulting mixture was then stirred for an additional 40 minutes until substantially all of the solids were dissolved before being cooled to 50 °C.

Example 5: MIC of Shampoos against *Pityrosporum ovale* and *Candida albicans*

The shampoos of Examples 1 through 5, as well as two comparative commercial shampoos, were investigated for their *in vitro* activity against five strains of *Malassezia furfur* ATCC numbers 42132, 44337, 44340, 44342 and 44343 and one strain of *Candida albicans* H 29. Comparative shampoos "A" is a 0.5% coal tar-containing anti-dandruff shampoo available from Neutrogena Corporation, under the tradename "T-Gel," and comparative shampoo "B" is a 1% ketoconazole-containing anti-dandruff shampoo available from Neutrogena Corporation under the tradename "Neutrogena Long Lasting Dandruff Control Shampoo".

The shampoos were diluted directly into the culture medium, Diagnostic Sensitivy Test agar (DST ; Oxoid, UK) with the addition of Tween 80 (2 ml/l) and glyceryl monostearate (2.5 g/l) to give concentrations of 0.1 to 40 % of the shampoos in the culture medium. Consequently, the minimum inhibitory concentration (MIC) values are for the whole shampoo, and not only the active ingredient(s). As used herein, " MIC" means the lowest concentration of the shampoo at which a total inhibition of microorganism growth was observed.

The microorganisms were added onto the agar medium-filled plates in concentrations of 10^7 cell/ml (*Malassezia furfur)* and 10^6 cells/ml (*C. albicans*). These plates were incubated at 37°C and read after 1, 2 and 3 days. All shampoos were tested in duplicate. The MIC results are presented in Table 2 below:

Table 2 MIC of Shampoos of Examples 1 Through 4

	M. furfur ATCC 42132	*M. furfur* ATCC 44337	*M. furfur* ATCC 44340	*M. furfur* ATCC 44342	*M. furfur* ATCC 44343	*C. albicans* H. 29
Ex. 1: Shampoo Base	1%	1%	2.5%	1%	2.5%	20%
Ex. 2: Base & Dichlorophenyl imidazoldioxolan at pH 4	0.1%	0.1%	0.5%	0.1%	0.5%	1.0%
Ex. 2 Base & Dichlorophenyl imidazoldioxolan at pH 7	0.1%	0.1%	0.1%	0.1%	0.1%	0.5%
Ex. 3: Base, Salicylic Acid, & Piroctone olamine	0.5%	0.5%	0.5%	0.5%	0.5%	0.5%
Ex. 4: Base, Dichlorophenyl imidazoldioxolan , Salicylic Acid, & Piroctone olamine	0.1%	0.1%	0.1%	0.1%	0.1%	0.5%
Comp. A: T-Gel	2.5%	2.5%	2.5%	2.5%	2.5%	10%
Comp. B: 1% Ketoconazole	0.1%	0.1%	0.1%	0.1%	0.1%	0.5%

As illustrated in Table 2 above, we have surprisingly found that the effectiveness of the shampoo containing dichlorophenyl imidazoldioxolan, piroctone olamine, and salicylic acid (Ex. 4) in prohibiting the growth of *M. furfur* is equivalent to that of the ketoconazole-containing shampoo (Comp. B) and is superior to that of the coal tar-containing shampoo (Comp. A).

With respect to prohibiting the growth of *C.albicans*, we have further surprisingly found that the effectiveness of the shampoo containing dichlorophenyl imidazoldioxolan/piroctone olamine/salicylic acid (Ex. 4) is equivalent to that of the ketoconazole-containing shampoo (Comp. B). and is superior to that of the coal tar-containing shampoo (Comp. A)

In sum, it is evident that shampoos containing dichlorophenyl imidazoldioxolan, and in particular those containing dichlorophenyl imidazoldioxolan /piroctone olamine/salicylic acid (Ex. 4) are significantly more effective against the growth of both *M. furfur* and *C.albicans* relative to other commercial shampoos.

Example 6: MIC of Shampoos against *Malassezia furfur*

The shampoos of Examples 5, as well as an additional comparative commercial shampoo, were investigated for their *in vitro* activity against twenty-nine strains of *Malassezia furfur*. Comparative shampoo "C" is a 2% ketoconazole-containing anti-dandruff shampoo available from Janssen Pharmaceutica N.V. under the tradename "Nizoral". The shampoos were diluted 50-fold in sterile water, then further diluted in sterile water to generate a dilution series in two-fold concentration steps.

Twenty-nine isolates of *Malassezia furfur* yeasts collected from people with and without dandruff or seborrhoeic dermatitis were maintained on a modification of Dixon agar comprising, based upon a liter of distilled water: 36 g of malt extract available from Difco Laboratories; 6 g of Oxoid mycological peptone obtained from Unipath, Ltd.; 20 g of bacto-oxgall obtained from Difco Laboratories; 10 ml of polysorbate 40 available from ICI Americas, Incorporated under the tradename "Tween 40;" 2.5 ml of glycerol; and 20 g of agar. Dixon broth is composed of the same but without the agar.

Inocula were then prepared by growing the yeasts for 2 days at 30 °C in glass test tubes (diameter = 13mm) containing Dixon broth and sterile glass beads and rotating the cultures at 20 rpm. Suspensions were standardized to an optical density of 1.0 at 530 nm by adding sterile water thereto. The optical density was measured with a model UV-160A Shimadzu spectrophotometer and a 1 cm light path.

50 µl of a 33-fold dilution of the resulting inoculum suspension was added to 50 µl of each sample shampoo dilution in a flat-bottomed plastic microdilution plate, which resulted in a final shampoo dilution series starting from 1:100.

After incubating the resulting cultures in an incubator for 4 days at 30 °C, the optical density of the wells was read with a model 3550 Bio-Rad automatic plate reader set at 570 nm. The growth (turbidity) of the M. furfur in the presence of the sample shampoos was

caculated as a percentage of growth turbidity in drug-free control wells for each isolate. The maximal inhibitory dilution of a product for an isolate of *M. furfur* was defined as the highest dilution of test shampoo that reduced growth below 50% of control according to the spectrophotometric readings. The maximal inhibitory dilution results are presented in Table 3 below.

Table 3: Cumulative Percentage of Isolates Inhibited

Dilution	Comp. C	Ex 3	Ex 4	Ex 2 (high pH)	Ex 2 (low pH)	Ex 1	Comp. A	Comp. B
3276800	0	0	0	0	0	0	0	0
1638400	0	0	0	0	0	0	0	0
819200	0	0	0	3	0	0	0	0
409600	0	0	0	7	3	0	0	0
204800	24	0	41	41	59	0	0	0
102400	59	0	100	100	93	0	0	17
51200	100	0	100	100	100	0	0	59
25600	100	0	100	100	100	0	0	100
12800	100	0	100	100	1000	0	0	100
6400	100	0	100	100	100	0	0	100
3200	100	0	100	100	100	0	0	100
1600	100	0	100	100	100	0	0	100
800	100	3	100	100	100	0	0	100
400	100	17	100	100	100	17	0	100
200	100	100	100	100	100	86	0	100
100	100	100	100	100	100	97	97	100
<100	100	100	100	100	100	100	100	100
N=	29	29	29	29	29	29	29	29

It is evident from Table 3 that all three shampoos which contained dichlorophenyl imidazoldioxolan showed very strong inhibitory activity against *M. furfur in vitro*, inhibiting 90% of the 2090 test isolates at a dilution of 1:102400. This Examples shows that compositions containing dichlorophenyl imidazoldioxolan effectively inhibited the growth of *M. furfur*, a microorganism that is believed to contribute to hyperkeratotic scalp disorders, and thus would be effective in formulations for treating the same.

Example 7: MIC of Formulations against *Propionibacterium acnes*

Culture mediums were prepared in accordance with the procedure set forth in Example 5, but with formulations of dichlorophenyl imidazoldioxolan in water instead of shampoos.

After *P. acnes* were added onto the agar medium-filled plates in concentrations of about 10^7 cell/ml , the plates were incubated and read in accordance with the procedure set forth in Example 5. This Example was repeated using two additional, different strains of *P. acnes*.

The resulting MIC, which in this example is the lowest concentration of the dichlorophenyl imidazoldioxolan at which a total inhibition of microorganism growth was observed, was 1 mg/ml for two strains and 10 mg/ml for the third strain. This Example shows that dichlorophenyl imidazoldioxolan is active against the growth of microorganisms involved in the pathogenesis of acne.

Example 8: Comparative Testing of Elubiol, Salicylic Acid, and Benzoyl Peroxide

One hundred and seven adults, 32% of whom were male, who ranged in age from 14 to 31 years old and had nearly identical levels of acne symptoms, were assigned to apply a given cream twice a day for 12 weeks. Approximately one third of the group applied a 0.1% Elubiol-containing cream available from Penaten G.m.b.H. under the tradenames "BeBe Rein und Klar Gel" ("E Cream"); approximately another third of the adults applied a 2% salicylic acid cream available from Johnson & Johnson Consumer Companies, Inc. under the tradename, "CLEAN AND CLEAR Invisible Blemish Treatment" ("SA Cream"); while the remaining adults applied a 10% benzoyl peroxide cream available from the Procter & Gamble Company under the tradename "Clearasil Maximum Strength Vanishing Cream" ("BPO Cream").

Before treatment began, the baseline absolute lesion count, i.e. count for total comedones, open comedones, closed comedones, papules, pustules, cysts, and nodules, was calculated for each adult. Each adult was also given a rating on a qualitative scale from 0 (absent) to 3 (severe) for baseline acne symptoms, i.e. oiliness, erythema, dryness, peeling, burning, stinging, itching and tightness. Each adult was further rated for its baseline acne level, i.e. Grade I (comedonic acne); Grade II (papular-pustular acne) or Grade III (acne conglobata). At baseline, all adults were classified as having Grade II acne and as having nearly identical levels of acne symptoms. After 1, 2, 4, 8, and 12 weeks of treatment according to this regime, the absolute lesion count, the acne symptoms, and the acne level for each adult were recalculated.

After treatment began, the total comedone count dropped significantly versus baseline for all of the adults. The decrease was fastest in the group using the BPO Cream,

with a 46% decrease after 2 weeks. The group treated with the E Cream also had an 8% decrease after 2 weeks, while the group treated with SA Cream only had a 2% decrease in the number of comedones.

After 12 weeks, the group treated with BPO Cream had a 67% reduction in comedone count, while the groups treated with E Cream and SA Cream had a 36% and a 37% reduction, respectively. A similar pattern was observed for both open and closed comedones.

This Example showed that the cream containing 10% benzoyl peroxide had a comparatively faster and more pronounced effect against comedones relative to creams containing either the .1% elubiol or 2% salicylic acid. This Example further showed that elubiol tended to have a somewhat faster onset of action than salicylic acid.

The cream containing 10% benzoyl peroxide also showed the fastest and more pronounced response against papules, with final lesion counts reduced by about 2/3 for users of the BPO Cream versus 1/3 for the other two groups. Pustules, cysts, and nodules were rarely seen in any of the adults.

Within 1 week after the start of treatment, the group using the BPO Cream showed a 75% reduction in oiliness, versus a 55% reduction for users of the E Cream and a 35% reduction for users of the SA Cream. At the end of the 12 week treatment period, the elubiol treated group had a decrease in oiliness of 73%, versus decreases of 51% and 71% for salicylic acid and benzoyl peroxide, respectively.

Erythema decreased by 39% within 1 week after the start of treatment in the elubiol group, versus a 30% decrease with salicylic acid and a 13% increase with benzoyl peroxide. At the end of the 12 weeks, erythema was reduced by 48%, 48% and 55% in the 3 groups, respectively. This Example showed that, in comparison to baseline values, only the elubiol treated patients shown significant reduction in erythema from the first week onwards.

During the first two weeks of treatment, the irritation scores were more pronounced for adults in all groups. After the initial 2 week period, signs of irritation were reduced. At the end of the 12 weeks, the elubiol group showed the least amount of irritation (0/3.0), versus apparent irritation in the salicylic acid group (0.3/3.0) and the benzoyl peroxide group (0.38/3.0). This Example showed that the highest level of irritation was seen in the benzoyl peroxide group, followed by the salicylic acid group, and the elubiol group.

Dryness and peeling were also assessed on the same severity scale. In particular, the benzoyl peroxide group showed a significantly greater amount of dryness and peeling than the salicylic acid group or the elubiol group.

Stinging did not prove to be a problem with any of the users, and itching improved during the course of the study in the 3 groups. The fastest reduction in itching was observed in the group using the E cream.

Skin tightness was not much of a problem initially, but it became noticeably worse in the group using the BPO cream during the first weeks of treatment.

In sum, this Example showed that the 0.1 percent elubiol cream was comparatively faster acting and more efficacious than the 2% salicylic acid cream. While the .1 percent elubiol cream was not as fast-acting as the 10% benzoyl peroxide cream, the elubiol cream had comparatively minimal side effects and was better tolerated overall by the users than the benzoyl peroxide cream.

Claims

We claim:

1. A method for treating seborrheic dermatitis, dandruff, and psoriasis comprising:
   a) applying to skin or hair an effective amount of a composition comprised of
      1) dichlorophenyl imidazoldioxolan; and
      2) a therapeutic component selected from salicylic acid, coal tar and derivatives thereof, piroctone olamine, selenium sulfide, ciclopirox olamine, and mixtures thereof.

2. The method of claim 1 wherein said therapeutic component is salicylic acid.

3. The method of claim 2 wherein said therapeutic component is further comprised of piroctone olamine.

4. The method of claim 1 wherein said dichlorophenyl imidazoldioxolan and said therapeutic component are present in quantities effective for inhibiting the growth of fungi.

5. The method of claim 1 wherein said dichlorophenyl imidazoldioxolan is present in an amount, based upon the total weight of the composition, of from about 0.25% to about 2% and said therapeutic component is present in an amount ranging from about 0.5 % to about 3 %.

6. A composition comprising:
   a) dichlorophenyl imidazoldioxolan; and
   b) a therapeutic component selected from salicylic acid, coal tar and derivatives thereof, piroctone olamine, selenium sulfide, ciclopirox olamine, and mixtures thereof.

7. The composition according to claim 6 wherein said component is salicylic acid.

8. The composition according to claim 7 further comprising piroctone olamine.

9. The composition according to claim 6 wherein said dichlorophenyl imidazoldioxolan and said therapeutic component are present in quantities effective for producing a mutual synergistic effect on the inhibition of the growth of dermatophyte fungi.

10. The composition according to claim 6 wherein said dichlorophenyl imidazoldioxolan is present in an amount, based upon the total weight of the composition, of from about 0.25% to about 2% and said therapeutic component is present in an amount ranging from about 0.5 % to about 3 %.

11. An article of manufacture containing the composition according to claim 6.

12. The article of manufacture of claim 11 which is a shampoo.

13. The article of manufacture according to claim 11 further comprising one or more of the following components:

a.) at least one surfactant;

b.) a foaming agent;

c.) a thickener sufficient to give the final formulation a viscosity in the range of about 4,000 to about 9,000 mPa.s at room temperature;

d.) a preservative;

e.) an anti-oxidant; and

f.) an acid or base or buffer sufficient to give the shampoo a pH in the range of from about 3 to about 8.

14. The article of manufacture according to claim 11 further comprising one or more surfactants selected from the group comprising sodium C14-16 olefin sulfonates, sodium lauryl sulfate, sodium laureth sulfate, cocamidopropylamine oxide, lauryl amine oxide, lauramido DEA, cocamidopropyl betaine, lauryl dimethyl betaine, cocodimethyl sulphopropyl betaine, sodium cocoyl sarcosinate, disodium oleamido MIPA sulfosuccinate, disodium cocamido MIPA sulfosuccinate, disodium laureth sulfosuccinate, cocoamphocarboxy-glycinate, disodium oleamido MEA sulfosuccinate, amine glycinates, amine propionates and amine sultaines, or mixtures thereof.

15. The article of manufacture of claim 11 wherein said surfactant is comprised of from about 4% to about 12 % of an anionic surfactant and from about 3% to about 10% of an amphoteric surfactant.

16. The article of manufacture of claim 11 wherein said anionic surfactant is comprised of sodium olefin sulfonate, sodium lauryl sulfate, sodium laureth sulfate or mixtures thereof, and said amphoteric surfactant is comprised of cocamidopropylamine oxide, cocamidopropyl betaine or mixtures thereof.

17. The article of manufacture of claim 11 wherein said foaming agent is selected from fatty acid mono- and di- alkanolamides comprising cocamide MEA, cocamide DEA, oleamide MEA, oleamide DEA or mixtures thereof.

18. The article of manufacture of claim 11 wherein said antioxidant is butylated hydroxytoluene, butylated hydroxyanisole, ascorbic acid, N-acetyl cysteine, sodium metabisulfite or a mixture thereof employed in an amount, based upon the total weight of the shampoo, of from about 0.01 to about 1 %.

19. The article of manufacture of claim 11 further comprising a conditioner.

20. The article of manufacture of claim 11 further comprising one or more pearlizing agents comprised of ethylene glycol distearate, ethylene glycol monostearate or mixtures thereof.

21. An article of manufacture containing the composition according to claim 7.

22. An article of manufacture containing the composition according to claim 8.

23. A process for preparing a body and hair cleansing formulation comprising:

(a) mixing an anionic surfactant and deionized water under conditions sufficient to produce a first mixture;

(b) mixing dichlorophenyl imidazoldioxolan and antioxidant with said first mixture under conditions sufficient to produce a second mixture;

(c) cooling said second mixture to a sufficient temperature before the addition of a therapeutic component thereto;

(d) mixing said therapeutic component with said cooled second mixture under conditions sufficient to produce a third mixture;

(e) mixing a buffer and an amphoteric surfactant with said third mixture under conditions sufficient to produce a fourth mixture.

24. The process of claim 23 wherein said anionic surfactant is comprised of sodium olefin sulfonate, sodium lauryl sulfate, sodium laureth sulfate, or mixtures thereof.

25. The process of claim 23 wherein said amphoteric surfactant is cocoamidopropylamine oxide or mixtures thereof.

26. The process of claim 23 wherein said therapeutic component is salicylic acid.

27. The process of claim 26 further comprising the addition of piroctone olamine to said third mixture.

28. The process of claim 23 further comprising cooling said fourth mixture.

29. The process of claim 28 further comprising adding a conditioner to said fourth mixture under conditions sufficient to produce a conditioned fourth mixture.

30. The process of claim 23 further comprising adding a second amphoteric surfactant to said conditioned fourth mixture.

31. The process of claim 30 wherein said second amphoteric surfactant is cocamidopropyl betaine or mixtures thereof.

32. A method for inhibiting the growth of bacteria on the surface of skin comprising:

topically applying to the skin an effective amount of a composition comprised of dichlorophenyl imidazoldioxolan.

33. The method of claim 32 wherein said composition is further comprised of a therapeutic component selected from salicylic acid, coal tar and derivatives thereof, piroctone olamine, selenium sulfide, ciclopirox olamine, and mixtures thereof.

34. A method of treating acne, tinea capitis, and tinea corporis comprising:

topically applying to the skin an effective amount of a composition comprised of dichlorophenyl imidazoldioxolan.

35. The method of claim 34 for treating acne.

36. The method of claim 35 wherein the composition is comprised of, based upon the total weight of the composition, from about 0.1 percent to about 2 percent of dichlorophenyl imidazoldioxolan.

38. The method of claim 35 wherein the composition is further comprised of salicylic acid.

39. The method of claim 38 wherein the composition is comprised of a weight ratio of dichlorophenyl imidazoldioxolan: salicylic acid of from about 0.5:2.0 to about 1:1.

40. A method of relieving one or more of the following symptoms of the skin or scalp: itching, redness, or erythema comprising:

topically applying to the skin an effective amount of a composition comprised of dichlorophenyl imidazoldioxolan.

41. The method of claim 40 wherein the composition is further comprised of salicylic acid.

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/US 98/13425

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K7/06 A61K7/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 93 18743 A (JANSSEN PHARMACEUTICA N.V. ET AL.) 30 September 1993 see page 1 - page 2 see page 4, line 29 - page 5, line 15	1-31,33, 38,39,41
X		32, 34-36,40
Y	WO 96 29983 A (COLGATE PALMOLIVE COMPANY ET AL.) 3 October 1996 see the whole document	1-31,33, 38,39,41
A	US 4 335 125 A (HEERES ET AL.) 15 June 1982 see column 17, line 1 - line 19 see column 10, line 41 - line 61	
A	US 5 456 851 A (JUE-CHEN LIU ET AL.) 10 October 1995	

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 October 1998	05/11/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alvarez Alvarez, C

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INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/US 98/13425

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. .onal Application No
PCT/US 98/13425

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